What's New in Prostate Cancer, Benign Prostatic Hyperplasia, and Minimally Invasive Surgery?

Highlights from the XIXth Congress of the European Association of Urology, March 23-27, 2004, Vienna, Austria

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The XIXth Congress of the European Association of Urology, held in Vienna, Austria, March 23-27, 2004, underscores the increased support across Europe toward the Annual Meeting of European Urologic Surgeons.

There was, as usual, predominance in abstract submissions dealing with prostate cancer, benign prostatic hyperplasia, and minimally invasive surgery, and these, together with other popular topics, made for an interesting program of scientific presentations. Following is a review of a selection of abstracts on the above topics.

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Prostate Cancer

Basic Research, Growth Factors / Tumor Biology / Novel Therapies, Androgen Receptors / Apoptosis

Low serum testosterone (T) levels are associated with high-grade prostate cancer (PCa). Inhibin is a major secretory product of the prostate epithelium and its expression may be altered in benign and malignant tissues and cell lines. In addition, inhibin has an inhibitory influence on pituitary gonadal axis. Maerk and colleagues[1] studied whether low serum T levels are associated with higher serum levels of inhibin. In men with untreated verified prostate cancer, an endocrine study including testosterone (T), sex hormone binding globulin (SHBG), follicle stimulating hormone (FSH), luteotropic hormone (LH), prostate-specific antigen (PSA), and prostate volume was performed. In addition, serum inhibin (subunit beta) was measured.

A total of 86 men were included in this study. Twenty-seven men had a serum T level of 3 ng/mL (group 1). These men had significantly lower levels of LH (4.5 ± 2.4 mIU/mL vs 5.8 ± 2.8 mIU/mL; $P = .03$) and estradiol (24 ± 7 pg/mL vs 33 ± 8 pg/mL; $P = .02$) compared to the group that had a serum T level of greater than 3 ng/mL (group 2). In group 1, the median Gleason score (25%; 75% interquartile range [IQR]) was 6 (5/7). There was no significant difference in age, PSA, prostate volume, and FSH. The serum level of inhibin in group 1 was similar to group 2 (153.8 ± 72.4 pg/mL vs 164.9 ± 62.9 pg/mL). There was a significant negative correlation of inhibin to FSH ($r = – .448$; $P < .001$) and to LH ($r = – .287$; $P = .01$) and of T to Gleason score ($r = – .237$; $P = .03$).

The authors showed a significant correlation of inhibin to LH and FSH, but no significant difference between the groups with low and normal serum T levels; therefore, inhibin should not play a key role in hypoandrogenism in men with PCa.

Kuratsukuri and colleagues[2] used a model system to target a defined region of the extracellular domain of prostate-specific membrane antigen (PSMA) for experimental immunotherapy of prostate cancer. Prostate-specific membrane antigen is a surface antigen expressed by prostate epithelium that is upregulated approximately 10-fold in most prostate tumors. The authors vaccinated BALB/c mice with NIH3T3 cells cotransfected with pST/neo plus pEF-BOS based vectors expressing either the full-length 750-amino acid human PSMA or only the C-terminal 180-amino acid region (PSMc). PSMc lays C-terminal to the transferring receptor-like sequence in the extracellular domain of PSMA. BALB/c mice were injected IP 4 times at weekly intervals with vaccine cells. Vaccinated mice were then challenged SC with Renca/PSMA, a BALB/c renal cell carcinoma line transfected to express human PSMA.

Growth of Renca/PSMA tumors was substantially retarded and host survival significantly prolonged in mice prevaccinated with either 3T3/PSMA or T3/PSMc. Furthermore, antiserum from vaccinated mice intensely immunocytochemically stained LNCaP, a PSMA-positive human prostate cancer cell line. In contrast, control mice similarly prevaccinated IP with 3T3/neo (NIH3T3 cells transfected with pST/neo alone) developed Renca/PSMA tumors, which were palpable within 2 weeks and lethal by 5 weeks. Serum from 3T3/neo-vaccinated mice did not immunocytochemically stain LNCaP cells. The antitumor activity induced by vaccination with 3T3/PSMc was also demonstrated via growth inhibition of established LNCaP tumors xenografted in athymic mice following passive transfer of immune serum from vaccinated mice.

Fullerton and coworkers concluded that a targeted gene therapy approach with radiolabeled MIGB may produce a promising new treatment for prostate cancer.

These results suggest that vaccination with PSMc induces adaptive humoral activity, which is directed against the extracellular region of human PSMA and can significantly inhibit human prostate cancer growth in athymic mice, and that administration of antibodies to PSMA may provide a passive treatment modality for immunocompromised patients.

Fullerton and colleagues,[3] from Glasgow, presented data on targeted radiotherapy, which is the selective irradiation of tumors by radionuclides conjugated to tumor-seeking molecules, such as meta-iodobenzylguanidine (MIBG), which is actively taken up by cells expressing the noradrenaline transporter (NAT).

Introduction of the NAT transgene into prostate cancer cells under the control of tumor-specific telomerase promoters should allow them to take up radioiodine-labeled MIBG with resulting cell kill of the transfected cells and neighboring tumor cells that have escaped transfection (radiological bystander effect).

A targeted radiotherapy approach to prostate cancer could decrease side effects from radiation toxicity, allowing increased radiation dose to target organs, leading to improved cure rate.

The authors demonstrated that, in vitro, NAT gene transfected cells exhibited a significantly increased uptake of [^{131}I] MIBG, which correlated with cell kill. Clonogenic assays performed in spheroids, a 3-dimensional model, demonstrated a powerful bystander effect. In vivo, biodistribution studies postinjection of [^{131}I] MIBG showed preferential uptake of [^{131}I]MIBG in organs rich in noradrenergic innervation, and markedly increased uptake in tumors expressing NAT. The authors concluded that expression of a functional NAT after in vitro transfection of prostate cancer cells with the NAT gene under the control of telomerase promoter is possible, leading to active uptake of [^{131}I]MIBG and dose-dependent cell kill. The in vivo tumor xenograft model confirmed the selective biodistribution of [^{131}I]MIBG uptake. A targeted gene and radiotherapy approach with radiolabeled MIBG may produce a promising new treatment for prostate cancer.

Wolfram and colleagues,[4] from the University of Vienna, Austria, evaluated the apoptotic behavior of prostate cancer cell lines in vitro and identified biological response modifiers involved. Recently, CD95 has been shown to regulate apoptosis of breast cancer cell lines in vitro.

Cultivated prostate cancer cells from radical prostatectomy specimen as well as cell lines such as DU145, LNCaP, and PC3 were cultured in RPMI 1640 medium supplemented with 10% fetal calf serum (FCS). Tumor cells were incubated with interleukin-6 (IL-6) and tumor necrosis factor α (TNF-α) and CD95L (all: 1 mg/mL) for 24, 48, and 72 hours. Apoptosis was measured by flow cytometry.

The conclusion was that the combination of the cytokines TNF-α and IL-6 with CD95L did induce a significant

apoptotic response, especially in androgen-independent prostate cancer, suggesting a future role in the treatment of androgen insensitivity and cancer recurrence.

Kramer and associates[5] investigated the possibilities offered by high-intensity focused ultrasound (HIFU) in the field of tumor vaccination, and analyzed how PCa cells react towards heat treatment and whether increased access to PCa cells by the immune system would be the result. The authors have studied the heat/stress response of PCa cells in situ and of PCa cell lines by immunohistochemistry, Western blotting, and Atlas array. A heat-induced change in immune recognition was analyzed functionally using T-helper (Th) 1 and Th2-cytokine release with tumor infiltrating T-lymphocytes (TIL) as responder and autologous PCa cells either heated or untreated as stimulator cells.

Transcription of 68 out of 500 genes was upregulated by sublethal heat in LNCaP and PC3 cells. Significantly upregulated stress protein expression (heat shock protein [HSP]-72, -73; glucose regulated protein [GRP]-75, -78) was seen at the border zone of HIFU treatment. Remarkably, even untreated benign prostatic hyperplasia (BPH) specimens revealed relative overexpression of HSP72, -73, and GRP75, -78. Heated PCa cells increased Th1 cytokine (IL-2, interferon-α [INF-α]) release, but decreased Th2 cytokine (IL-4, -5, -10) release of TIL.

Kramer and associates comment that HIFU treatment may alter the presentation of prostate tissue and tumor antigens and that this presentation is most likely stimulatory. HSP72, -73 overexpression in untreated BPH may suggest a mechanism by which BPH can incite inflammation.

Novel Markers / Prostate-Specific Antigen / Molecular Markers

Therapy escape and progression of prostate cancer is associated with enhanced survival signals and resistance to induction of apoptosis (programmed cell death). Myeloid cell lymphoma 1 (Mcl-1) is an anti-apoptotic protein of the Bcl-2 family, which functions in the regulation of apoptosis.

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Pfeil and colleagues[6] investigated the role of Mcl-1 in prostate cancer, employing measurement of expression in tumor specimens and regulation of expression in the LNCaP prostate cancer progression model. Tissue specimens were obtained from prostate cancer patients undergoing radical prostatectomy and from palliative transurethral resections performed after development of hormone-resistant cancer. Tissue expression levels were determined by immunohistochemistry and visual inspection by the pathologist using a 4-point scoring scale for number of positive cells and intensity of staining. The lymph node metastasis–derived LNCaP prostate cancer cell line and the long-term androgen ablated sublines LNCaP-abl and LNCaP-abl HOF — the latter 2 representing advanced prostate cancer— were used to analyze regulation of expression of Mcl-1 by Western blot. Apoptosis was measured by determining a caspase cleavage fragment.

Mcl-1 was expressed in 67% of the investigated malignant prostatic tissue specimens from radical prostatectomy and the majority of samples obtained after escape from hormonal therapy by palliative transrectal surgery. However, Mcl-1 was detected in only 6% of the corresponding benign specimens. Comparison of nonmalignant epithelial prostate cells with metastatic cancer cell lines showed an increase of Mcl-1 expression in the tumor cells. Regulation of expression involves the protein kinase B (PKB) survival pathway. Mcl-1 levels decrease after inhibition of PKB in LNCaP cells.

Most interestingly, this downregulation is not seen in the long-term androgen ablated LNCaP-abl cells. Surprisingly, overexpression of Mcl-1 did not increase the resistance to apoptosis, underscoring the importance of a regulatory network in this process.

The authors concluded that Mcl-1 overexpression is an early event in prostate cancer, suggesting it as a potential target for tumor therapy. This is accompanied by dysregulation of expression during progression in the LNCaP model. For future use it will be important to understand its interplay with the other proteins that regulate the induction of apoptosis.

Caglia and coworkers[7] studied the biological effects of growth factor targeting. Erb-B2 is a member of the epidermal growth factor receptor family. Its ligand is not known, but this protein represents the preferred heterodimerization partner for the other members of the family. Many cancers present hyperexpression of Erb-B2. Moreover, its role in androgen receptor activation has been recently demonstrated. These data explain the interest in targeting Erb-B2. The aim of this study was to evaluate the biological effects of diminishing Erb-B2 expression. The authors analyzed the expression of Erb-B2 in LNCaP, DU-145, and PC-3 cell lysate by Western blotting. Then they verified the

phosphorylation of this receptor in response to treatment with a monoclonal antibody directed against the extracellular portion of Erb-B2 (trastuzumab) by Western blot. Finally, they used 2 different approaches to diminish Erb-B2 expression: (1) treatment with trastuzumab and (2) RNA interference by introduction of small interfering RNA (siRNA) into the cells with a retroviral vector.

Their findings suggest that Erb-B2 is highly expressed by LNCaP and DU-145 cell lines and, in these cell lines, its basal level of phosphorylation increases in response to trastuzumab treatment. The Western blot analysis demonstrates the diminished expression of Erb-B2 in response to trastuzumab treatment and siRNA introduction for RNA interference. Both techniques can decrease the PSA production in LNCaP cell culture. The PSA concentration in cell culture media is an optimal read-out of AR activation. LNCaP treated with siRNA directed against Erb-B2 presents a lower growth rate than LNCaP wild type.

Caglia and colleagues demonstrate that target therapy against Erb-B2 in prostate cancers, which hyperexpress this protein, is effective.

The experimental data demonstrate that the decreased expression of Erb-B2 in the LNCaP cell line can diminish the androgen receptor activation and, thus, PSA production, like the growth rate of these cells. This suggests the efficacy of target therapy against Erb-B2 in prostate cancers, which hyperexpress this protein.

Prostate-Specific Antigen Derivatives and New Technologies / Genetics and Gene Therapy

An interesting idea was tested by Irani and colleagues.[8] Because previous studies reported that the ratio of urinary PSA to total serum PSA (U/S) improves the detection of men with prostate cancer, the authors tested this hypothesis by evaluating the clinical usefulness of the U/S PSA ratio and comparing it to the free-to-total (F/T) serum PSA ratio.

One hundred sixty-five patients undergoing transrectal ultrasound-guided prostate biopsy were prospectively included in this multicenter study. Prostate-specific antigen was measured preoperatively (Kryptor assay) in all patients from serum and 12-hour urine specimens in a centralized laboratory.

Among the 165 patients, 83 (50.3%) had prostate cancer identified on their biopsy. Differences between patients without and with prostate cancer were statistically significant ($P < .001$; Mann-Whitney test) when considering total PSA (median values 10.2 ng/mL and 6.6 ng/mL, respectively), F/T serum PSA ratio (.18 and .11, respectively) or U/S PSA ratio (4.2 and 1.2, respectively).

In the group of patients with a PSA between 4 and 10 ng/mL (79 patients, including 33 with cancer), receiver operating characteristic (ROC) curves showed that the U/S PSA ratio was associated with a larger area under the curve (AUC; 63; 95% confidence interval [CI], .51-.73) than total PSA (.55; 95% CI, .43-.66) or F/T serum PSA ratio (.60; 95% CI .49-.71). U/S PSA ratio was correlated neither with patients' age nor with prostate volume. The U/S PSA ratio was not correlated with the F/T serum PSA ratio. When using a threshold of 6.8 (according to the ROC curve), PSA ratio brought additional information to F/T serum PSA ratio. The number of cancer and noncancer patients for a U/S PSA ratio threshold of 6.8 among 37 patients in a gray zone for F/T serum PSA ratio ($.12 < F/T \text{ ratio} < .22$) were as follows: no cancer (n = 22, 9 with U/S PSA ratio < 6.8 and 13 with ratio ≥ 6.8), cancer (n = 15, 13 with U/S PSA ratio < 6.8 and 2 with ratio ≥ 6.8).

The results confirm that U/S PSA ratio may be a useful test in prostate cancer detection when total serum PSA is between 4 and 10 ng/mL. Free-to-total serum PSA ratio and U/S PSA ratio are not correlated. This suggests that these tests could complement each other, particularly when F/T serum PSA ratio is in the gray zone.

The aim of the prospective multicenter European Prostate Cancer Detection trial was to test the value and diagnostic performance of the molecular forms and indices of PSA and their derivates in combination with prostate gland and transition zone volumes in detection of prostate cancer in men with PSA levels between 2 to 4 ng/mL.

Reissigl and associates[9] reported on a total of 413 men with a total serum PSA (tPSA) between 2 and 4 ng/mL (age range, 36–82 years) who were included in this prospective European trial between November 2001 and August 2003. In all patients, the ratio of complexed PSA (cPSA) to tPSA (c/tPSA), cPSA density (cPSAD), cPSAD of the transition zone, PSA, free PSA (fPSA), ratio of fPSA to tPSA (f/tPSA), tPSA density (PSAD), and PSAD of the transition zone were measured. tPSA and fPSA were analyzed with the AxSYM® test (Abbott Laboratories, Abbott Park, IL), whereas cPSA was measured with the ACS:180® cPSA Bayer assay (Bayer Corp., Tarrytown, NY).

All men underwent transrectal ultrasound-guided sextant prostate biopsies and 2 additional transition zone biopsies.

Two hundred ninety-nine patients had noncancer histology, whereas 114 were diagnosed with prostate cancer (72.3% and 27.7%, respectively). Significantly larger total and transition zone (TZ) volumes were noted in men with benign disease (P = .0051 and P = .0071, respectively).

At 90% and 95% sensitivity, specificity of cPSA was significantly greater than for tPSA (P < .0001). At sensitivity levels of 90% and 95%, the specificity of cPSA assay using cutoff values of 1.80 and 1.50 ng/mL was 16.8% and 10.5%, respectively. A cPSA cutoff value of 3.0 ng/mL and 3.5 ng/mL afforded 90% and 95% specificity for detecting prostate cancer. The AUC of cPSA was significantly higher than tPSA (60.7 vs 54.6, P = .070). In addition, AUC for c/tPSA and volume-related parameters PSAD, PSAD of the transition zone, cPSAD and cPSA-TZ of the transition zone were 63.3%, 63.5%, 65.6%, 67.2%, and 70.4%, respectively.

In the low PSA range, cPSA outperformed tPSA in the differentiation between benign disease and prostate cancer. C/tPSA was slightly superior to f/tPSA ratio.

In addition, cPSA-volume–related parameters (cPSAD, cPSAD of the transition zone) further improved the specificity of PSA in early detection of prostate cancer. Considering equal results to PSA parameters in the intermediate PSA range, cPSA may primarily become a cancer detection marker for the low PSA range (< 4 ng/mL).

Remzi and colleagues,[10] from the University of Vienna, Austria, have evaluated power Doppler in transrectal ultrasound (PD-TRUS)-guided biopsy. To determine the utility of PD-TRUS–guided prostate biopsies in men with PSA levels between 2.5 and 10 ng/mL and to evaluate the impact on PCa detection in men undergoing first and repeat biopsies, the authors studied a total of 136 consecutive men with serum total PSA levels between 2.5 and 10 ng/mL (mean age 64 years; range, 45–82). One hundred one patients underwent first biopsy and 35 underwent a repeat biopsy. Gray-scale TRUS and PD-TRUS (B-K Medical, Denmark) were obtained in the lithotomy position prior to and during biopsy. Vascularity accumulation and perfusion characteristics were recorded and were judged as normal or abnormal in the peripheral zone of the prostate. In all patients, a Vienna nomogram–based biopsy plus additional biopsies for abnormal sites on PD-TRUS were performed.

An abnormal accumulation on PD-TRUS was identified in 42.6% and 46.8% on first and repeat biopsy, respectively. Overall PCa detection rate was 35% and 25.7% on first and repeat biopsy, respectively. The PCa detection rate on first and repeat biopsy in patients with and without power Doppler ultrasonography (PDU) accumulation was 67.4% versus 10.3% (P < .001, Fisher exact test) and 47.05% versus 5.9% (P = .0049, Fisher exact test), respectively. Only PDU-directed biopsies were positive in 5.7% and 11.1% on first and repeat biopsy. PCa detection without PD-TRUS-directed biopsies was 94.3% and 88.9% on first and repeat biopsy. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of PDU signal for PCa detection on first biopsy was 82.8%, 78.8%, 87.9%, and 89.7%, respectively, and on repeat biopsy 88.8%, 68.0%, 47.0%, and 94.4%, respectively, whereas PD-TRUS–guided biopsies reached on first biopsy only 53.8%, 59.1%, 16.7%, and 89.5%, respectively, and on repeat biopsy only 20.0%, 13.3%, 23.5%, 11.1%, respectively.

The PD-TRUS signal seems to be able to exclude a major part of patients without PCa in the PSA range of 2.5 to 10 ng/mL, as PCa detection in the PDU signal negative patients was only 10.3% and 5.9% on first and repeat biopsy. However, PD-TRUS–guided prostate biopsy failed to enhance prostate biopsy strategy.

Transrectal prostatic tumor thermal ablation with HIFU is an alternative treatment of prostate cancer in nonsurgical patients. To evaluate the complications of transrectal HIFU (Ablatherm®, EDAP TMS, Vaulx-en-Velin, France) for the treatment of localized prostate cancer, Rozet and associates,[11] from Institut Montsouris, Paris, France, evaluated 261 patients with localized prostate cancer. Fifteen patients were previously treated with external beam radiation. For 10 patients, laparoscopic ilio-obturator lymphadenectomy had been performed previously.

One hundred seventy-four patients had undergone previous transurethral resection of the prostate (TURP) in order to decrease the risk of postoperative urinary retention. The mean age was 72 years (range, 61–79). The mean prostate weight was 30 g (range, 11–45), and the median PSA level was 7 (range, 1–10). The mean number of positive biopsies was 2/6, and the median Gleason score was 6 (range, 4–7). Three patients died at 26, 32, and 43 months from a pulmonary embolism, a myeloma, and a myocardial infarction, respectively. One obese patient with a previous

Remzi and colleagues evaluated power Doppler in transrectal ultrasound-guided biopsy, and found that its signal seems to exclude a majority of patients without prostate cancer in the PSA range of 2.5 to 10 ng/mL.

laparoscopic lymphadenectomy suffered from a pulmonary embolism. Eighty percent of patients had gross hematuria that spontaneously cleared in the following 15 days. A urinary infection was diagnosed by urine culture in 60 patients. Twelve patients presented with urethral stenosis and were treated endoscopically (8/12) or with dilatations (4/12).

In 87 patients treated with Ablatherm and without previous TURP, 8 patients underwent a TURP between 1 and 15 months postoperatively, 2 had symptoms of dysuria related to elimination of retained necrosed prostate fragments, and 1 developed a bladder stone on a retained prostate fragment. Thirty-four patients are now stress incontinent, 19 had minimal leakage without protection, 13 had moderate leakage with 1–3 pads/day, and 2 had severe leakage, necessitating an artificial sphincter in 1 patient at 1 year. Fifteen percent of patients complained of urgency during the first month postoperatively. No anal leakage was reported. Patients with normal preoperative erectile function complained of impotence (35%) and erectile dysfunction (12%) between the first and 18th month posttreatment.

In one study, Rozet and associates have concluded that Ablatherm® preceded by TURP is well tolerated without major complications.

The authors have concluded that Ablatherm preceded by TURP is well tolerated without major complications. Respecting the inferior limit of the apex is mandatory in order to decrease the risk of incontinence.

On the same issue, Gelet and associates,[12] from Lyon, France, evaluated if nadir PSA can also be considered a predictive factor in HIFU therapy for localized prostate cancer. For radiation treatments, either external or interstitial, it was established that nadir PSA has a strong predictive value for long-term patient outcome.

They treated their patients with HIFU as primary care for localized prostate cancer; patients with a baseline PSA level less than or equal to 30 ng/mL and with at least 1 year follow-up were included in this analysis. They were treated using the Ablatherm HIFU device. Patient follow-up included sextant biopsies and PSA level measurements. Any positive biopsy or 3 consecutive increases in the PSA level were considered as a failure for the disease-free rates (DFR) calculation.

Two hundred forty-two patients fulfilled these criteria and were considered for analysis. The mean patient follow-up was 28 ± 21 months (range, 12–108 months). The population description before HIFU was mean age 71 ± 5.4 years, mean prostate volume 32.4 ± 16.6 cc, mean PSA level 9.2 ± 5.8 ng/mL, and all had positive biopsies. The clinical stage was T1 for 118 patients, T2 for 115 patients, and T3 for 9 patients. Neoadjuvant hormones were administered to 33 patients. The DFR were calculated using the Kaplan-Meier method. For the overall population, the mean nadir PSA was .63 ± 1.30 ng/mL, and further follow up evidenced an 81% negative biopsy rate and a 63% actuarial DFR at 60 months. These results were stratified according to the disease-related risk and the initial nadir PSA level (Table 1).

Table 1
Nadir PSA as a Predictive Factor for Localized Prostate Cancer

Nadir PSA	n	Negative Biopsy Rate	DFR at 60 Months
< .5 ng/mL	172 (71%)	88%	74%
.5–1 ng/mL	27 (11%)	67%	53%
> 1 ng/mL	43 (18%)	65%	36%
		$P < .0001$	$P < .0001$

Reprinted from Gelet et al[12] with permission from the European Association of Urology.
DFR, disease-free rate; PSA, prostate-specific antigen.

Adjuvant treatment with external radiation (19 patients), hormones (19 patients), or a combination of both (2 patients) was administered to 40 patients (17%) presenting with rising PSA level with or without residual positive biopsies. For 17 patients with positive biopsies (10.2%), watchful waiting was justified due to the low (mean, 1.02 ng/mL) and slowly rising PSA level (mean velocity, .31 ng/mL/y).

The nadir PSA seems to be a valuable prognostic factor after HIFU treatment, obtained within 3 months after the procedure. Control biopsies are nevertheless still needed to verify the local efficacy and indicate if a HIFU retreatment should be considered.

Turkeri and Ozyurek,[13] from Marmara University in Turkey, have reported on the possible role of vitamin D receptor gene polymorphism in familial prostate cancer. Recent investigations provided evidence suggestive of vitamin D as an important determinant of prostate cancer risk. Similarly, common polymorphism in vitamin D receptor gene has recently been reported to be important in prostate as well as breast cancers. This study aimed at defining the association of such polymorphism in a cohort of patients and their first-degree relatives.

The authors analyzed vitamin D receptor gene polymorphism in a group of patients with prostate cancer (n = 56), their first-degree relatives (sons of patients, n = 35), and a control group (n = 19) comprised of patients undergoing surgical treatment for lower urinary tract symptoms with a final histological diagnosis of BPH. Polymerase chain reaction (PCR)–based TaqI restriction fragment length polymorphism (RFLP) analysis was made on peripheral blood samples and 3 genotypes (tt, Tt, and TT) were determined.

Results of this study did not confirm the previous reports indicating that polymorphism in vitamin D receptor gene might be an important determinant of prostate cancer risk. Possible explanation of this conclusion can be that different polymorphisms other than the TaqI site may be effective in different populations. It is also possible that the effects of inherited polymorphisms may be heavily modulated by a variety of environmental factors.

Epidemiology and Screening

Prostate cancer screening is controversial. A positive family history is one of the strongest risk factors for developing prostate cancer.

Herkommer and colleagues,[14] from the University of Ulm, Germany, investigated the rate of detected PCa in persons with or without a positive family history. A total of 846 first-degree relatives (brothers) of patients with or without a positive family history and 261 control persons were asked to undergo a screening test for prostate cancer. They were informed about PCa in general and their own PCa risk. Four hundred ninety-five brothers of PCa patients underwent a screening test: 110 PCa patients had a sporadic PCa diagnosed at an age younger than 56 years (young sporadic group), 174 had a sporadic PCa diagnosed at an age older than 55 years (older sporadic group), and 211 had a familial PCa (familial group). These data were compared to screening data of 118 control persons (control group). The screening consisted of a digital rectal examination in 100%, a PSA test in 90%, and a transrectal ultrasound in 79% of controls. The mean age of the screened persons was between 56 and 62 years in all groups. For the rate of detected PCa, a 95% CI was calculated. To compare PCa detection rates between groups screened, the chi-square test was used.

The authors concluded that a history of even 1 first-degree relative with PCa significantly increases the probability of detecting PCa in a screening examination, especially in relatives of younger PCa patients. The risk is highest for persons with a history of familial prostate cancer.

Herkommer and associates concluded that a history of even 1 first-degree relative with prostate cancer significantly increases the probability of detecting prostate cancer in a screening examination, especially in relatives of younger prostate cancer patients.

Berger and associates[15] evaluated the effects of PSA screening with low PSA cutoff values on mean total and percentage free PSA levels in patients with prostate cancers at the time of diagnosis, on PSAD and TZ density, as well as on mean Gleason scores in positive biopsies and radical prostatectomy specimens. Moreover, the correlation between serum percentage free PSA and Gleason scores of radical prostatectomy specimens was calculated. The authors collected data from 1188 patients who were diagnosed with prostate cancers between 1995 and 2003. Patients were stratified into 8 groups according to the year of biopsy. Annual changes in total and percentage free PSA values, in Gleason scores of biopsies and radical prostatectomy specimens, and in PSA density and TZ density were assessed.

Mean PSA of patients diagnosed with prostate cancer decreased from 10.6 ng/mL (% free PSA, 10.25%) in 1995 to 4.7 ng/mL (% free PSA, 13.80%) in 2003 ($P < .05$). Mean PSAD and mean PSAD-TZ decreased from .331 to .131 ($P < .05$) and from .976 to .243 ($P < .05$), respectively. However, mean Gleason scores increased from 4.54 to 6.25 in prostate biopsies and from 5.65 to 6.38 in radical prostatectomy specimens over the 8 years ($P < .05$). No correlation was found between serum percentage free PSA and Gleason scores of radical prostatectomy specimens.

Prostate-specific antigen screening with low cut-off levels has led to a significant reduction of mean baseline PSA levels in prostate cancer patients and to a significant decrease of PSAD and PSAD-TZ, whereas mean Gleason scores have increased over the years. Because baseline PSA levels have a significant influence on the rate of organ-confined prostate cancers, these findings support the concept of PSA screening with low PSA cutoff levels.

Early Diagnosis / Prostate Biopsy / Staging

High-grade prostatic intraepithelial neoplasia (hg-PIN) is generally accepted to be a precursor lesion of prostate cancer. A prospective 6-month follow-up study of 100 patients with hg-PIN was performed by Joniau and associates[16] to investigate the effects of a short-term chemoprevention scheme on PSA and clinical management.

In a 2-year period, 100 men were

included in a prospective trial, evaluating the effects of short-term selenium-vitamin E-isoflavonoid supplements in patients diagnosed with hg-PIN on octant biopsies of the prostate. Twenty-four patients refused further biopsies; 76 underwent a second set of biopsies at 3 months (V2) and 62 underwent a third set of biopsies at 6 months (V3). In all but 4 patients (23/27) in whom prostate cancer was found on V2 or V3 biopsies, a radical prostatectomy was done.

Mean age at inclusion was 62.7 years (range, 43–80 years) and mean total PSA was 5.63 ng/mL (range, .23–31.9 ng/mL). At V2, a decrease in PSA from baseline was observed in 64% of patients. In this group, prostate cancer was found in 12.2% of men. In a further 36% of patients, an increase in PSA from baseline was noticed. In this group, prostate cancer was found in 29.6% of men.

At the end of the study (V2 + V3), cancer was found in 35.5% (n = 27) of men, hg-PIN in 39.5% (n = 30), isolated low-grade (lg)-PIN in 14.5% (n = 11), and no PIN or carcinoma in 10.5% (n = 8). The risk of finding cancer throughout the whole of the study was 26.5% in the group with a PSA decrease from baseline (64% of patients) and 51.9% in the group with a PSA increase from baseline (34% of patients). In patients who underwent a radical prostatectomy (n = 23), pathological stage ranged from foci of microinvasive carcinoma to pT3a. Gleason scores ranged from microinvasive carcinoma to Gleason score 8. In the V2 group (n = 13), all but 1 patient had organ-confined cancers (1 was pT3), 53.8% had a Gleason score of 7 or more, and the incidence of significant cancers (volume of .5 mL or more) was 69.2%. In the V3 group (n = 10), all cancers were organ-confined, 90% had a Gleason score less than 7, and 60% were insignificant cancers (volume < .5 mL).

In the present group of patients diagnosed with hg-PIN and on a selenium-vitamin E-isoflavonoid supplement, the risk of finding prostate cancer in a 6-month follow-up period was 35.5%. Interestingly, in a large subgroup (64%), PSA decreased under supplement therapy. In this subgroup, the overall risk of finding cancer was only 26.5%, compared to 51.9% in a smaller subgroup of patients (36%) in whom the PSA continued to rise under supplements. Thus, careful PSA monitoring is mandatory in patients with hg-PIN who are on supplement therapy. A selenium-vitamin E-isoflavonoid supplement is probably only of interest for those patients with a PSA response. Long-term studies are required to further validate this observation.

Prostate biopsy should be performed as quickly as possible to decrease symptoms and this is a major argument against periprostatic nerve blockade.

Dias and colleagues,[17] from Portugal, have reported on the increasing tendency to perform local anesthesia before TRUS-guided biopsy of the prostate. Recently, 2 anesthetic techniques have been described—topical lidocaine gel and ultrasound-guided periprostatic nerve blockade (PPB). In our view, prostate biopsy should be performed as quickly as possible to decrease symptoms and this is a major argument against PPB. The infiltration can, itself, induce pain and implies a longer procedure. The aim of this study was to assess the efficacy of topical anesthesia with lidocaine gel during TRUS-guided biopsy.

A randomized, blind placebo-controlled prospective study reported on patients who submitted to first or repeated TRUS-guided biopsy; 6 to 16 fragments were collected. Patients were divided into 3 groups: group 1 patients submitted to transrectal lidocaine gel (Instillagel®; Farco-Pharma GmbH, Cologne, Germany) administration 5 minutes before the biopsy; group 2 patients submitted to transrectal administration of nonanesthetic gel (ultrasound gel) 5 minutes before the biopsy; and group 3 patients were not submitted to any administration. Standard TRUS-guided biopsy was performed.

Patients were assessed by means of a self-questionnaire after leaving the room where the technique was performed. Pain and discomfort were assessed with a visual analogical scale. Two hundred forty-two consecutive patients who submitted to TRUS-guided biopsy were evaluated. The mean number of fragments was equivalent for all groups. The mean score of pain in group 1 patients was significantly inferior to pain scores in groups 2 and 3. The same results were found in discomfort scores. No differences were found between groups 2 and 3. An even higher difference was obtained when more than 8 fragments were collected and in cases of repeated biopsies.

The results of this study demonstrate that transrectal lidocaine gel administration (Instillagel) is a quick, practical, painless, noninvasive technique for anesthesia during TRUS-guided biopsy, and it is very efficacious in reducing pain. It permits a significantly shorter time of probe insertion. The authors concluded that in their view, it should be the preferred technique for anesthesia during TRUS-guided biopsy.

Khan and colleagues[18] have addressed the prognostic staging value of the percentage of positive cores in

TRUS-guided biopsy of the prostate. Recently it was shown that the percentage of cores infiltrated by cancer powerfully predicts margin status, pathological status, and future biochemical failure. However, in the United Kingdom, practical and simpler parameters are desirable to cut down on pathologists' time and expense. The authors examined the percentage of cancer-positive biopsy cores in addition to clinical stage, PSA, and Gleason grade for the prediction of pathological stage and surgical margin status.

A total of 280 of 362 patients between 1992 and 2003 from 2 UK centers had complete preoperative staging information, including the percentage of cancer-positive biopsy cores. Patients underwent either radical perineal or retropubic prostatectomy for localized prostate cancer, performed by 1 of 2 leading surgeons. Logistic regression was employed.

Age (P = .049), PSA (P = .008), and percentage positive biopsy cores were significant predictors of capsular penetration but not of clinical stage (P = .41) and biopsy Gleason grade (P = .065). The model predicted with a sensitivity of 50%, a specificity of 83%, a positive predictive value (PPV) of 67%, and a negative predictive value (NPV) of 70%. Likelihood ratio was 3 (1.97–4.36). Only PSA (P = .012) and percentage positive biopsy scores (P = .001) were predictors of seminal vesicle invasion. Model classification was excellent with a likelihood ratio of 16.5 (4.7–57.3; sensitivity 21%, specificity 98%, PPV 66.6%, NPV 91.2%). Likewise, only PSA (P = .005) and percentage positive biopsy cores (P < .0001) were predictors of margin status with a likelihood ratio of 4.7 (2.6–8.5; sensitivity 35%, specificity 92%, PPV 70.4%, NPV 74.2%). The authors concluded that percentage of biopsy cores positive for cancer predicts postoperative stage and margin status in a UK population. This parameter is easy to obtain by the clinician and is a substitute for the time-consuming estimation of percentage biopsy tissue infiltrated by cancer or involved by Gleason grade 4/5. This adds to the information available to select and counsel patients prior to radical surgery.

Haese and colleagues,[19] from Hamburg, Germany, have validated an algorithm for preoperative prediction of lymph node (LN) metastases in clinically localized PCa. The authors applied this algorithm to sextant biopsy material and radical retropubic prostatectomy (RRP) stage obtained from a cohort of men treated at their institution. A total of 443 patients underwent systematic sextant biopsy and RRP and staging lymphadenectomy. The original algorithm was based on systematic sextant biopsy data and classified patients into 3 risk groups for LN metastases based on the biopsy result. If more than 4 out of 6 biopsies contained any Gleason pattern 4 cancer, the patient was at high risk for LN metastases (45%). Patients with more than 1 out of 6 biopsies with dominant Gleason pattern 4 cancer (excluding high-risk patients) had an intermediate predicted risk (19%) of LN metastases. All other patients had a low predicted risk of LN metastases (2.2%). The authors assessed the percentage of patients positive and negative for LN metastases and calculated specificity and NPV in their series when patients were classified according to the original algorithm.

From 443 patients, 20 had intraoperative LN metastases. The Hamburg algorithm classified 404 patients in the low-risk group, 30 patients in the intermediate-risk group, and 9 patients in the high-risk group. The incidence of LN metastases in the low-risk group was 2.47%, in the intermediate-risk group 20%, and in the high-risk group 44.4%. The negative predictive value of the low-risk group was 97.52% and the specificity was 94.14%.

The authors concluded that their Hamburg algorithm proved a valid tool for prediction of lymphatic spread in this validation on single institution data. It may serve as a tool to select those patients who do not need pelvic lymphadenectomy at radical prostatectomy, hence reducing morbidity and expenses. More importantly, with the increasing number of men undergoing treatment options where lymph node dissection is not performed, this validated algorithm provides an important selection basis regarding the appropriateness of a therapy that does not routinely include lymph node staging.

Haese and colleagues concluded that their Hamburg algorithm for preoperative prediction of lymph node metastases proved a valid tool for prediction of lymphatic spread.

Localized Prostate Cancer / Outcomes and Adjuvant Therapies

In the era of PSA testing, the likelihood of detecting prostate cancer by surgery (TURP or adenomectomy) decreased from 50% to 6%.

Bader and colleagues[20] addressed the question of whether these incidental prostate cancers should be treated by radical prostatectomy or whether watchful waiting would be advisable given that these tumors may be harmless.

They evaluated tumor stage, grading, lymph node involvement, and outcome of patients with incidental carcinoma of the prostate and radical prostatectomy.

They identified 92 patients who underwent radical prostatectomy within 3 months from incidental finding of prostate cancer after an initial negative transrectal biopsy. The percentage of incidental PCa in relation to the PSA level was 25% (PSA < 2 ng/mL), 16% (PSA 2–4 ng/mL), 7% (PSA 4–6 ng/mL), and 3% (PSA > 6 ng/mL), respectively. No residual tumor could be found in the prostatectomy specimen in 34 patients (37%), and 40 patients (44%) had localized prostate cancer. However, 18 patients (20%) had a locally advanced carcinoma and in 3 patients (3%) lymph node involvement could be detected. Most of the pT0 prostatectomy specimens (29/34 = 85%) had been classified as G2 prostate cancer, 3 (9%) as G1, and 2 (6%) as G3 in the initial histology. During follow-up, 7 patients developed tumor progression and 6 patients died of prostate cancer. The authors concluded that two thirds of the patients with incidental carcinoma of the prostate showed residual tumor in the prostatectomy specimen. In the remaining 37%, no residual tumor could be detected, but there are no reliable criteria to identify these patients; therefore radical prostatectomy is justified in all patients with incidental prostate cancer because it gives them a chance of cure.

Augustin and associates[21] reported on the biochemical failure rate after radical prostatectomy between prostate cancers affecting the TZ and those purely in the peripheral zone (PZ), when pathological tumor stage, Gleason score, and surgical margin status were comparable. The 5-year biochemical recurrence rate of 307 patients without neoadjuvant or adjuvant therapy was evaluated. A serum PSA level more than .1 ng/mL was defined as biochemical failure, whereas TZ cancers were considered when more than 50% of the cancer area was located in the TZ, and pure PZ cancers were situated completely in the PZ. Sixty-three TZ cases were matched to pure PZ cancers by comparable pathological tumor stage, Gleason score, and surgical margin status. The probability of biochemical cure was estimated by the Kaplan-Meier method, on a mean follow-up of 43 ± 17.1 months and 43.7 ± 16.9 months in patients with TZ cancers and pure PZ cancers, respectively. Matched pair analysis revealed a significantly ($P < .001$) higher prostatic antigen (14.8 vs 8.4 ng/mL) and a significantly ($P < .001$) higher tumor volume (8.2 vs 3.8 cc) of TZ cancers compared to pure PZ cancers. Kaplan-Meier analysis revealed an 80% actuarial cure rate of TZ cancers versus 89% of pure PZ cancers. The authors concluded that despite the significantly higher mean PSA values and tumor volumes, prostate cancers located in the TZ showed no different biochemical recurrence rate following radical prostatectomy than did PZ cancers, when cancers of both locations were matched by comparable pathological tumor characteristics. Thus, the postoperative prediction of biochemical failure would not be improved by the knowledge of cancer location.

Jeschke and colleagues concluded that laparoscopic SLA using a specially designed gamma probe with a 90º lateral energy window is feasible and detects micrometastasis.

In general, lymph node dissection (LND) in PCa is only considered as a staging procedure. Positive lymph node involvement is an unfavorable prognostic factor in patients with prostate cancer, whereas pelvic lymphadenectomy traditionally involves obturator fossa alone.

Perineural invasion (PNI) may be a route for prostate cancer dissemination, and the presence of PNI predicts disease recurrence after radical prostatectomy on univariate but not multivariate analysis. Recently, Maru and colleagues,[22] in the United States, have shown that the maximum diameter of PNI, rather than its mere presence, is an independent predictor of disease recurrence over and above Gleason score, PSA, and pathological stage. Khan and coworkers[23] tried to determine if maximum diameter of PNI was also important in patients from the United Kingdom.

The maximum diameter of PNI found in the radical prostatectomy specimen was analyzed from 107 patients treated between 1994 and 2000. Exclusion criteria included neoadjuvant hormonal therapy or adjuvant therapy before evidence of treatment failure. Perineural invasion diameter, Gleason score, pretreatment PSA, and pathological stage were compared with evidence of disease recurrence (PSA > .4 ng/mL, local/systemic progression, onset of adjuvant treatment). Kendall tau was used to calculate correlation and medians were used to describe central tendencies for patient characteristics.

Patient characteristics (N = 107) were PSA 8.9 ng/mL (mean), Gleason score 7, pathological stage T3a, and positive margin rate 23%, and median follow-up was 29 months. The median PNI diameter was .315 mm (interquartile range .25–.4 mm). The diameter of PNI was correlated with Gleason score ($P = .21$, 95% CI, .01-.33), pathological stage ($P = .35$, 95% CI, .25-.453) but not PSA ($P = .16$, 95% CI, – .025-.29). On univariate Cox proportional hazards regression, Gleason score ($P = .004$), pathological stage ($P = .0001$), and PNI diameter ($P = .04$) were associated with disease recurrence. Patients with a PNI diameter in excess

of .8 mm were more likely to suffer from biochemical failure.

Findings suggested that PNI diameter is significantly associated with feature characteristics of disease failure and predicts biochemical failure following radical prostatectomy and that it is an independent variable predicting disease recurrence following radical prostatectomy.

Jeschke and associates[24] developed a technique that allows radioisotope-guided sentinel lymphadenectomy (SLA) in conjunction with laparoscopic radical prostatectomy (LRP).

Radioisotope-guided lymphadenectomy has been shown to increase the sensitivity of detection of micrometastasis in open pelvic lymphadenectomy by detecting positive nodes outside obturator fossa. From November 2001 to August 2003, SLA was performed preceding LRP in 40 patients with a mean age of 65 years (range, 47–75). Mean preoperative PSA was 9.16 ng/mL (range, 1.6 – 25.4 ng/mL). Twenty-four hours prior to surgery, a total of 3 mL colloid-containing Tc-99 m (200 MBq) was injected into 3 locations of each prostatic lobe. Scintigraphy was performed. A laparoscopic gamma probe, 10 mm in diameter with a lateral energy window at 90° specially designed for this purpose, was used (Ethicon, Austria). This enabled scanning of a large area with high spatial resolution, thereby compensating for the limited maneuverability of the probe, given the position of the trocars. Radioactivity was measured in situ prior and after SLA as well as within the removed nodes. The sentinel lymph nodes (SLN) were sent for frozen section and, if positive for micrometastasis, an extended pelvic lymphadenectomy was performed. Preoperative activity was seen on both sides in 31 (78%), unilateral in 8 (20%), none in 1 (2%), and postoperatively in 25 (63%), 14 (35%), and 1 (2%), respectively. In 50% of patients, SLN were exclusively outside the obturator fossa. Histopathologic examination showed micrometastasis to SLN in 4 (10%) patients. Seventy-five percent of this metastasis was outside the obturator fossa. Lymph node metastases were exclusively found in 99m-Tc marked lymph nodes. Postoperative PSA was 0 ng/mL in patients with negative SLN.

The authors concluded that laparoscopic SLA using a specially designed gamma probe with a 90° lateral energy window is feasible and detects micrometastasis.

Men who have been treated with radical prostatectomy usually go through follow-up with PSA controls at regular intervals. The means of localizing the relapse today are insufficient, consisting of digital rectal examination, transrectal ultrasound with random or directed biopsies, skeletal scintigraphy, computer-aided tomography, magnetic resonance tomography, or a combination of the above. However, there have been some reports, which included a relatively small number of patients, where positron emission tomography (PET) using acetate as a marker has shown to be promising.

One study concluded that PET with acetate as a marker to identify and localize prostate cancer cells is a promising and much-needed tool as the number of patients with PSA relapse continues to grow.

Ruiz and colleagues,[25] from France, reported on incontinence and impotence, which are frequent disorders after LRP. They have prospectively studied continence and potency after trans- and extraperitoneal LRP.

From 2000 to 2002, 330 men had a laparoscopic radical prostatectomy for localized prostate cancer, 165 by transperitoneal approach and 165 by extraperitoneal approach. They completed a confidential self-questionnaire about their micturition and sexual disorders before and 1 month, 3 months, and 6 months after surgery.

Before surgery, all patients were continent. Respectively for trans- and extraperitoneal approach, 93.1% and 96.1% patients were potent. Respectively 1 month, 3 months, and 6 months after surgery, diurnal continence was perfect (no pad, no leakage) in 14%, 48.2%, and 60% for transperitoneal approach and 14.1%, 34.9%, and 62.5% for extraperitoneal approach. Nocturnal continence was perfect in 21.5%, 56%, and 73.6% for transperitoneal approach and 16.7%, 46.5%, and 81.2% for extraperitoneal approach.

Respectively 1 month, 3 months, and 6 months after surgery, erection (potency allowing sexual intercourse without medication) was present in 24.4%, 26.3%, and 28% for transperitoneal approach and 14.7%, 20.9%, and 34.4% for extraperitoneal approach. Three months after surgery, in cases of bilateral preservation of neurovascular bundles, erection was present in 30.3% and 46.7%, respectively, for trans- and extraperitoneal approaches.

The authors concluded that continence seems to increase earlier after transperitoneal LRP, but seems to be better with extraperitoneal approach 6 months after surgery. Erection seems to be equivalent between the different approaches.

Lundin and colleagues,[26] from Uppsala, Sweden, evaluated this method, studying 10 prostatectomized patients (age 71 ± 3 years) with an increasing PSA measured at least twice. Prostate-specific antigen ranged from .5 to 5.3 ng/mL 10 minutes after intravenous injection of

approximately 800 MBq of carbon-11-acetate; the patients were examined in a Siemens HR+ scanner from the jugular notch to the perineum. An independent evaluation of the synthesized pictures was made considering pathological uptake at the locus of the prostate, the pelvis, the skeleton, and distant metastases.

In 80% of cases, pathological uptake of acetate was identified. Six of 10 cases showed uptake at the locus of the prostate (2 of these were found also with digital examination) and, overall, 3 patients had uptake in the small pelvic region, 3 patients showed skeletal uptake (2 patients were also scintigraphized but with a negative finding), and 1 case showed a distant metastasis (a lung cancer metastasis). The final conclusion was that PET with acetate as a marker to identify and localize prostate cancer cells is a promising and much-needed tool at a time when the number of patients with PSA relapse is growing as a consequence of the increasing frequency of radical treatments for men with prostate cancer.

These small numbers of patients investigated indicate a method with high sensitivity. Further studies will evaluate the actual clinical value of this method.

Transrectal ultrasound-guided biopsies of the anastomotic region remains a controversial method for detecting local recurrence following radical prostatectomy. Djavan and coworkers[27] evaluated, quantified, and validated a new power color Doppler-enhanced TRUS protocol for accurate prediction of early local recurrent cancer in a biopsy-controlled study.

Two hundred three consecutive men at 3 institutions, with biochemical recurrence at a mean of 28 months (range, 11–82 months) following radical prostatectomy were prospectively evaluated. A sextant TRUS-guided biopsy of the anastomotic region (B-K Medical, Denmark) was obtained routinely. Further follow-up parameters consisted of digital rectal exam, PSA, percentage free PSA, bone scan, and chest X-ray. During biopsy a newly developed TRUS Doppler imaging sequence was employed to guide the needle and evaluate features of local recurrence and benign prostatic or fibrotic tissue. A new quantifying Doppler scale was developed and employed. Results were prospectively compared to biopsy results and ROC curves and regression analysis was performed.

The newly developed power color Doppler flow-enhanced TRUS will allow a more appropriate detection of local recurrence with a sensitivity and specificity over 85% and 90%, thus eliminating the need for anastomotic biopsies.

Median recurrent PSA at the time of evaluation and biopsy of the anastomotic region was 1.5 ng/mL (range, .3–5.8 ng/mL). Sextant biopsy of the anastomotic region was obtained in all patients. Recurrent cancer was found in 31.5% of patients (64/203). Benign prostatic tissue only was found in 13.3% (27/203) and benign fibrotic tissue in 55.2% (102/203) of patients. Quantified perfusion characteristics differed in terms of quality, quantity, and perfusion pattern, with strongest signals for recurrent cancer (signal intensity [SI] = .89), benign prostatic tissue (SI = .61), and benign fibrotic tissue (SI = .09) in declining order. Perfusion pattern was circular and belt-like in cases of cancer recurrence and irregular in all other cases. Color Doppler-enhanced TRUS had a sensitivity and specificity of 81.3% and 90.6% (AUC = 85%), respectively, in predicting local cancer recurrence. Transrectal ultrasound color Doppler was the most powerful predictor of local recurrence as compared to time to recurrence (P = .002) and PSAD-TZ (P = .001).

Interestingly, a differing flow and impedance pattern was observed in patients with benign prostatic tissue at the anastomotic site as compared to those with recurrent cancer.

This newly developed power color Doppler flow (PCD)-enhanced TRUS will allow a more appropriate detection of local recurrence with a sensitivity and specificity over 85% and 90%, respectively, thus eliminating the need for anastomotic biopsies.

In the first analysis of the bicalutamide (Casodex®; AstraZeneca Pharmaceuticals, Wilmington, DE) Early Prostate Cancer (EPC) program (median 3 years' follow-up), bicalutamide 150 mg plus standard care (watchful waiting [WW], radical prostatectomy, or radiotherapy) significantly improved progression-free survival (PFS) compared with standard care alone.[28] Iversen and colleagues[29] report the results for the WW subgroup from the second protocoled analysis (median 5.4 years follow-up).

The EPC program consists of 3 geographically distinct double-blind placebo-controlled trials including 8113 men with T1-4, M0, and any N prostate cancer. In the WW subgroup (n = 2285), 1114 patients were randomized to bicalutamide 150 mg and 1171 to placebo. The PFS endpoint included objectively confirmed (by ultrasound, MRI, CT, or bone scan) progression or death from any cause. The hazard rate (HR) and event-time ratio (ETR) were calculated.[30]

Overall, 377 patients (33.8%) receiving bicalutamide 150 mg and 470 receiving placebo (40.1%) had objective disease progression. Compared

with placebo, bicalutamide 150 mg significantly reduced the risk of progression by 32% (HR, .68; 95% CI, .60-.78; $P < .0001$) and increased PFS by 31% (ETR, 1.31; 95% CI, 1.09-1.45). Exploratory analyses showed that although patients with localized disease derived significant benefit from bicalutamide 150 mg (HR, .81; 95% CI, .68-.96; $P = .018$), those with locally advanced disease had the greatest benefit (HR, .53; 95% CI, .42-.65; $P < .0001$). There was no difference in overall survival (OS) between treatment groups; however, planned statistical investigations suggested that the relative effect of bicalutamide 150 mg on OS may depend on disease stage at entry. Subsequent exploratory analyses indicate a trend towards improved OS in WW patients with locally advanced disease receiving bicalutamide 150 mg (HR, .81; 95% CI, .63-1.04; $P = .097$) and towards improved OS in WW patients with localized disease receiving placebo (HR, 1.23; 95% CI, 1.00-1.50; $P = .050$). The overall tolerability profile of bicalutamide 150 mg was consistent with that seen at 3 years' median follow-up, with the most common adverse events being gynecomastia (68.3%) and breast pain (73.6%).

The authors concluded that in patients who would otherwise receive WW, bicalutamide 150 mg significantly increases PFS, with those at higher risk of disease progression gaining the most benefit. There is no difference in OS at this point. Exploratory analyses indicate that in patients with locally advanced disease receiving bicalutamide 150 mg there is a trend towards improved survival, whereas for localized disease there is a trend towards a survival advantage in patients undergoing WW alone.

Hormonal Treatment / Quality of Life and Side Effects of Curative Treatment / Hormone Refractory Prostate Cancer

Bicalutamide monotherapy is a safe and effective treatment for selected prostate cancer patients who wish to avoid the effects of androgen deprivation but it causes gynecomastia and breast pain in a great majority of them. Conti and associates[31] investigated whether the addition of tamoxifen or anastrozole would prevent gynecomastia and breast pain without compromising treatment efficacy or safety and without interfering with patients' quality of life (QoL). The pharmacodynamics of each combination was also evaluated.

One hundred fourteen patients with localized or biochemically recurrent prostate cancer were entered in a double-blind placebo-controlled multicenter trial and randomly assigned to receive bicalutamide (150 mg/d) alone (group BP) or combined with either tamoxifen (20 mg/d) (group BT), or anastrozole (1 mg/d) (group BA).

Treatments were administered for 11 months or until disease progression or refusal; patients were periodically evaluated for the development of gynecomastia and mastalgia.

Effect of treatment on QoL and sexual functioning was investigated through a 30-item questionnaire. Serum levels of hormones, insulin-like growth factor 1 (IGF-1), and sex hormone binding globulin (SHBG) were also periodically evaluated. There were no differences concerning the scores relative to social functioning, emotional well-being, vitality, physical capacity, overall health, sexual interest, and sexual functioning, either at baseline or at 6 months. A sharp surge in testosterone levels occurred in each group but free testosterone levels remained unchanged in the BT group, due to the parallel increase of SHBG levels.

The addition of tamoxifen induced a significant decrease in both prolactin and IGF-1 levels.

The results suggested that tamoxifen was significantly more effective than anastrozole in preventing gynecomastia and mastalgia induced by bicalutamide. In addition, tamoxifen is safe and did not adversely influence PSA response or QoL. Cotreatment with tamoxifen appeared to prevent free testosterone surge and to induce a significant decrease in the serum levels of IGF-1 and prolactin, both of which are known to sustain prostate cancer growth.

Touijer and colleagues concluded that laparoscopic radical prostatectomy provides good short-term functional results for potency and continence.

Touijer and colleagues,[32] from Memorial Sloan-Kettering Cancer Center, New York, NY, have reported on how many patients can expect to be potent and/or continent at 3 months postoperatively following a laparoscopic radical prostatectomy. Three months postoperative potency and continence data were available on 85 consecutive patients who underwent laparoscopic radical prostatectomy for clinically localized prostate cancer.

Pre- and postoperative potency was graded with the following scale: I, normal full erections; II, full but diminished erections; III, partial erections, satisfactory for intercourse; IV, partial erections, unsatisfactory for intercourse; V, impotent. The surgeon also graded neurovascular bundle preservation immediately postoperatively as follows: preserved, possible damage, definite damage, and resected.

Pre- and postoperative continence was graded as: I, continent (no pads); II, mild stress urinary incontinence (SUI; leaks only with heavy physical

activity); III, moderate SUI (leaks with moderate activity); IV, severe SUI (leaks during normal activity, dry at night); V, total incontinence.

The conclusion was that laparoscopic radical prostatectomy provides good short-term functional results, with 53% of preoperatively potent patients having intercourse with or without sildenafil citrate at 3 months when both neurovascular bundles were preserved and with 75% of patients socially continent.

The nadir PSA is a predictive factor extensively used after radical treatments in prostate cancer. The nadir PSA has been associated with type of response and survival in patients with metastatic prostate cancer who received androgen deprivation therapy (ADT). Recently, it has been established that there is a relation between nadir PSA and androgen-independent progression (AIP). Esquena and colleagues[33] have evaluated the prognostic value of nadir PSA in AIP for a cohort of patients with metastatic prostate cancer who received ADT.

Their cohort consisted of 185 patients with prostate cancer T1-4 N0-1 M1 who received ADT (69 castration and 116 maximum androgen blockade). Median follow-up was 26 months and 164 (88.6%) events were detected. Androgen-independent progression was defined as 2 consecutive elevations of PSA above nadir. Univariate and multivariate analysis was used to define predictive factors to AIP and free time to AIP (+ 12 months). Gleason score, bone extension disease, pretreatment PSA, and PSA after 3 months of ADT, presence of hydronephrosis, type of ADT, nadir PSA and interval to achieve it were included as predictive variables.

Binary regression analysis showed that Gleason score, bone extension disease, and nadir PSA were independent prognostic factors to AIP at 12 months. However, the odds ratio (OR) for a nadir PSA less than 2 ng/mL was 4.6, whereas for Gleason score less than 7, OR was 3.5, and for bone extension disease with less than 6 hot spots, OR was 3.9. Cox regression analysis showed an OR for nadir PSA of 3.2, being greater than Gleason score and bone extension disease. An interval greater than 9 months until nadir PSA was also a significant predictive factor to AIP. The association of these prognostic factors stratifies patients into 4 different subsets according to the interval to AIP.

Dietary and nutritional factors may have an effect on benign prostatic hyperplasia etiology through a variety of mechanisms.

A nadir PSA of 2 ng/mL was the best predictive factor to AIP in patients with metastatic prostate cancer. An interval greater than 9 months to achieve a nadir PSA was also a good predictor to AIP. Finally, the association of these factors with the Gleason score and bone extension stratified patients with metastatic prostate cancer according to the prognosis.

In hormone refractory prostate cancer with metastases to the skeleton, the palliative efficacy of the strontium 89 (89Sr; Metastron™; GE Healthcare) and of the aminobisphosphonate olpadronate is well established. To date there are no studies comparing the efficacy or costs of the 2 agents. Soerdjbalie-Maikoe and associates,[34] from Leiden University, Leiden, The Netherlands, studied the clinical efficacy and costs of treatment of using the bone-seeking radionuclide 89Sr as compared to aminobisphosphonate olpadronate in the palliative management of patients with metastatic bone pain due to hormone refractory prostate cancer.

Fifty-six patients were randomized to receive either 89Sr chloride as a single injection of 150 MBq (4 mCi) or olpadronate IV as a single infusion of 20 mg diluted in normal saline followed by oral olpadronate at a dose of 200 mg/d (maintenance). Primary endpoints were changes in pain score, use of opiates, and overall QoL for the 3 months following treatment. Secondary endpoints were overall survival and health costs incurred with either treatment modality. Pain palliation was evaluated using a validated questionnaire for assessment of severity of pain. Use of analgesics, including opiates, was carefully recorded. Quality of life was evaluated by various scoring questionnaires including visual analogue scales (VAS) and World Health Organization (WHO) performance status scales. Cost analysis was undertaken for all healthcare costs incurred during the 3 months of the study.

Despite randomization, patients receiving olpadronate were significantly more symptomatic than those receiving 89Sr. A beneficial clinical response defined as a decrease in bone pain and/or a reduction in the use of opiates was observed in up to 60% to 75% of patients in both groups with no significant difference in clinical response between groups. With either treatment modality, mean survival was similar (about 7 months). At 3 months, there was no difference in pain palliation or QoL assessments between treatments. Costs of medication with olpadronate were less than those with 89Sr, but total healthcare costs were similar for both treatments because of the less frequent skeletal-related events (eg, spinal cord compression) using 89Sr.

The authors concluded that

olpadronate and 89Sr are equally effective in the palliative management of metastatic bone pain in hormone refractory prostate cancer. Skeletal-related events were less frequent in 89Sr-treated patients so that equivalent healthcare costs were attached to both treatment modalities.

Benign Prostatic Hyperplasia

Basic Research / Statistical Evaluation

The significance of the nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) pathway in the control of the human genitourinary tract has been well established. Recent research has demonstrated that pharmacological compounds known to interact with cyclic nucleotide–mediated pathways (eg, phosphodiesterase [PDE] inhibitors) reversed the contraction of prostatic strip preparations isolated from the transition zone.[35]

Heuer and coworkers,[36] from Hanover Medical School, Germany, and University of Innsbruck, Austria, examined the effects of PDE inhibitors and NO donors in a model of cultured human prostatic smooth muscle cells (PSMC).

The effects of the drugs on cell contraction and relaxation were determined by means of time-lapse video microscopy. Results have indicated that PSMC showed spontaneous contractions, while the number of contracting cells was significantly increased by endothelin-1 (ET-1). The ET-1–induced tension was reversed by the drugs with the following rank order of efficacy: forskolin > S-nitrosoglutathione (GSNO) > theophylline > sodium nitroprusside (SNP) > sildenafil > SW058237 (a dual PDE-4/PDE-5 inhibitor). The number of contracted cells was reduced by a degree of 80% by forskolin to 10% by SW058237.

The conclusion was that effects of NO donors and PDE inhibitors on PSMC contraction can be investigated on the cellular level using a cell culture model. The results were in support of the hypothesis that both cyclic adenosine monophosphate (cAMP) and cGMP contribute to the control of PSMC tension. These findings might provide a rationale for the future use of PDE inhibitors or NO donors in the pharmacotherapy of benign prostatic hyperplasia and lower urinary tract symptomatology.

Dietary and nutritional factors may have an effect on BPH etiology through a variety of mechanisms such as elevation of sympathetic nervous system activity and testosterone concentrations.

Mitropoulos and associates,[37] University of Athens, Greece, having reported notable alterations in the microscopic structure of the ventral prostate in hypercholesterolemic rats, examined the impact of heart disease on plasma sex steroid levels in rats.

Thirty male Wistar rats were fed, beginning at 120 days of age, for 5 months with either standard experimental animal food (15 animals) or standard food enriched with 4% cholesterol and 1% cholic acid. The body and ventral prostate weights (VPW), the plasma sex steroid levels, and lipid profile were determined.

The morphological changes of the prostate glands resembled those observed in experimental prostatic hyperplasia. Heart disease and subsequent hypercholesterolemia caused marked changes in sex steroids plasma profile in rats. Their findings suggest that hypercholesterolemia possibly alters prostate morphology by affecting the sex steroid axis and thus contributes to BPH pathogenesis.

Artificial intelligence has been serving as an alternative of traditional statistic analysis in many aspects of modern diagnostics or decision-making analysis.

Dobrovits and colleagues[38] have reported data based on a prospective longitudinal multicenter European study on watchful waiting in men with mild symptoms of bladder outlet obstruction (BOO), defined as having an International Prostate Symptom Score (IPSS) < 8, and a 5-year follow-up. A new artificial neural network was designed, trained, and validated, based on BPH-related clinical and biochemical parameters. The aim of the study was (1) to investigate correlations among clinical, biochemical, and urodynamic parameters, as well as total and TZ prostate volume, (2) to identify progression parameters in patients presenting with mild symptoms of BOO over a 5-year follow-up period, and (3) to identify and preselect patients at risk of progression/ nonprogression.

One author team concluded that artificial neural networks offer reliable tools in patients with prostate cancer and also improve patient selection in men with BPH.

The artificial neural network (ANN) used in the analysis was an advanced multilayer perceptron selected for accuracy by a genetic algorithm. A 10th-order cross validation methodology was used to ensure proper generalization (non-overfitting). Progression was included in the analysis and was defined as a change from the mild IPSS group into the moderate (IPSS 8–18) or severe (IPSS > 18) IPSS group or an increase in the IPSS score greater than 3 points. The occurrence of urinary retention or the need for surgery (TURP) was also qualified as disease progression. Quality-of-life scores were also recorded separately and cross-analyzed. Improvement was defined, based on the same criteria, in the reverse sense.

A total of 1208 patients who presented to 5 European university clinics for lower urinary tract symptoms (LUTS) due to BOO were included in this prospective longitudinal study. Patients with an IPSS less than 8 were identified and watchful waiting initiated. All were followed for up to 5 years at 3-month intervals. Measured parameters included age, PSA, IPSS, the total obstructive symptom score (OSS), the irritative symptom score (ISS), the quality-of-life score (QoL), and the maximal and mean flow rate; total (TPV) and transition zone (TZV) volume were recorded by TRUS for each patient.

Four hundred forty-six of 1208 men evaluated had mild symptoms of BOO (IPSS < 8) and 397 were available for follow-up at 5 years. Cumulative progression rate was 12%, 15%, 28%, 31%, and 39% at 12, 24, 36, 48, and 60 months, respectively; 60%, 65%, 73%, 71%, and 77% deteriorated without shifting to the next higher IPSS category. In contrast, improvement in symptoms was observed in 20%, 17%, 8%, 3%, and 2%, respectively at 1, 2, 3, 4, and 5 years, whereas 8%, 10%, 4%, 3%, and 2% had stable disease.

The overall accuracy of the ANN in predicting disease progression and the need for surgery was 76% and 80%, respectively. The variables of importance for disease progression in the ANN analysis were in order of significance: PSA cutoff of 2.0 ng/mL, OSS, age, and TZ volume. The combination of a PSA greater than 2 ng/mL and OSS offered an 86% accuracy. The variables IPSS, ISS, QoL, maximum flow rate (Qmax), and mean flow rate as well as postvoid residual volume (PVR) were not found to add significant predictive value. Overall accuracy was best in patients with PSA greater than 1.5 ng/mL.

The authors concluded that ANNs not only offer reliable tools in patients with prostate cancer, but also improve patient selection in men with BPH. In men with mild symptoms of BOO (IPSS < 8) under watchful waiting, progression rates to higher IPSS categories (8–18 and 19–35) increase from 12% at 1 year to 39% at 5 years. In those not shifting to a higher IPSS category, overall 70% will progress by at least 1 point. Improvement is observed in 20% at 1 year and decreases to 2% at 5 years. The ANN identified a PSA cutoff of 2 ng/mL, OSS, and age as best predictors of disease progression, overall symptomatic progression, rate of urinary retention, and need for surgery, respectively. The ANN was able to preselect patients at risk for disease progression with an overall accuracy of 86%.

One study concluded that long-term treatment with dutasteride results in continuing improvement of symptoms and peak urinary flow and that earlier initiation of dutasteride therapy results in greater improvements from baseline at 4 years.

Medical Therapy

Navarrete and colleagues[39] tested the potential effects of BPH pharmacology on: the age at which patients undergo surgery; preoperative prostate volume; complications due to BPH progression, such as acute urinary retention (AUR), urinary tract infection (UTI), bladder stone, hematuria, and hydronephrosis; type of surgery applied (TURP or open adenomectomy); the amount of tissue removed; complications of surgery; and average stay in the hospital. The authors compared the clinical profile (age, comorbidities, symptom severity, incidence of AUR), the type and duration of medical treatment, and indication for surgery of patients operated on in 1992 and in 2002.

This was a single-center retrospective cross-sectional observational study. The medical history of all patients who underwent BPH surgery in the first semester of 1992 (n = 85) and 2002 (n = 70) was reviewed. The preoperative clinical profile was assessed by looking at age, main comorbidities, prostatic volume, Qmax, and symptom severity. The type and duration of BPH pharmacology was evaluated by data contained in medical history and in phone calls. Indication for surgery was precisely evaluated, as was the type of operation and the weight of removed tissue (open adenomectomy) or the volume of the resected tissue (TURP). Surgical complications observed in both groups were stated, as was average stay in hospital. The results of this study indicate that BPH surgery was reduced 17.6% in a decade. Patients reach the operating room at a later age (69.12 ± 13.09 years vs 72.25 ± 13.58 years; 3.1 years older) but with similar comorbidities. Reasons for surgery in 1992 and 2002, respectively, were AUR in 41% and 37%, and symptom deterioration in 48% and 51%. The few cases of hematuria and bladder stones were similarly distributed in both groups. Benign prostatic hyperplasia pharmacology was used on 46% of patients in 1992, phytotherapy being the most common type (89%), whereas in 2002 82% of patients were treated, most of them with α-adrenergic antagonists (79%). Open surgery was indicated in 18.0% of patients in 1992 (average adenoma weight, 73.75 ± 19.04 g) and in 25.7% in 2002 (average adenoma weight, 79.8 ± 19.95 g). The volume of tissue resected by TURP was 34.67 ± 4.23 cc and 24.41 ± 3.52 cc in 1992 and 2002, respectively. Length of stay

in the hospital was 8.81 ± 1.09 days and 4.98 ± .72 days for 1992 and 2002, respectively, for TURP, and 14.06 ± 3.6 days and 8.7 ± 2.1 days for open adenomectomies. Rate of complications was similar for both groups.

The authors concluded that BPH patients are now operated on in fewer numbers with older age, after receiving medical treatment more often and for a longer period of time. Indications for surgery are similar. The most relevant finding in this series is that open surgery has to be applied more commonly than 10 years ago because the progressive increase in prostate volume was not affected by the medical therapy applied in this decade.

A good number of studies on BPH medical treatment were presented during the meeting. Dutasteride, a dual inhibitor of type 1 and type 2 5α-reductase, improves symptoms and urinary flow, and reduces prostate volume, the risk of AUR, and the need for BPH-related surgery. Debruyne and colleagues[40] presented results from an open-label extension study that provides 4 years of data to support the long-term efficacy and safety of dutasteride.

Patients who completed 2 years of randomized therapy with dutasteride (.5 mg) or placebo were eligible for a 2-year optional open-label extension study. Entry criteria for the double-blind portion included age older than 50 years, prostate volume greater than or equal to 30 cc, American Urological Association Symptom Index (AUA-SI) score greater than or equal to 12, Qmax less than or equal to 15 mL/s, and PSA greater than or equal to 1.5 ng/mL and less than 10 ng/mL. Efficacy measures were recorded at multiple time points. Results were presented from the open-label intent-to-treat population.

Four thousand three hundred twenty-five patients were randomized to dutasteride or placebo; 2340 patients received open-label dutasteride (1152 placebo/dutasteride [P/D], 1188 dutasteride/dutasteride [D/D]). Mean AUA-SI score and Qmax improved continuously in the D/D group over the 4-year study period. Changes from month 24 to month 48 were statistically significant ($P < .001$ for symptoms, $P < .01$ for Qmax). The P/D group treated with dutasteride between 24–48 months experienced improvements in AUA-SI and Qmax, but the improvements were not as great as in patients receiving dutasteride for 4 years ($P < .001$ for symptoms, $P = .042$ for Qmax) (Figure 1).

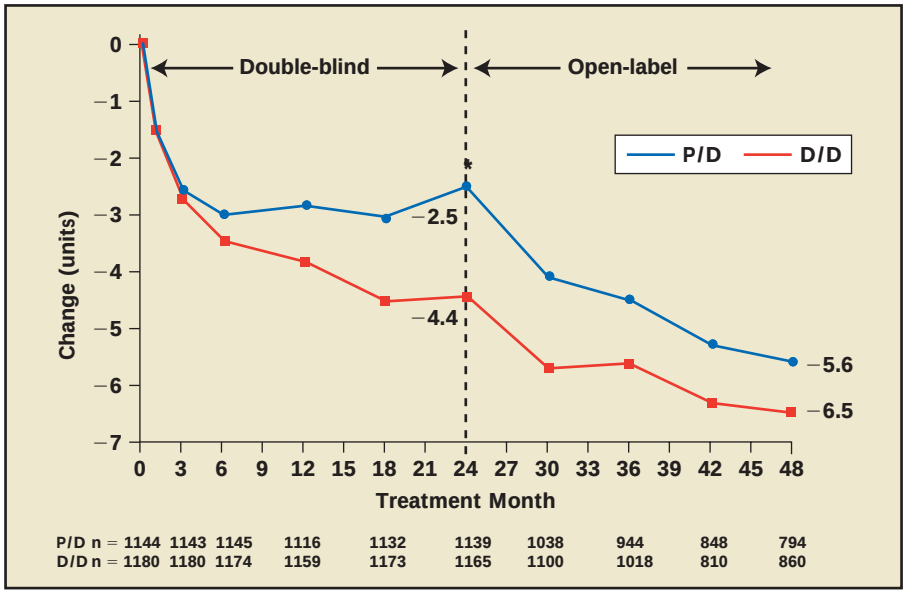

Figure 1. *Mean change in American Urological Assocation Symptom Index scores from baseline over 48 months. P/D, placebo/dutasteride group; D/D, dutasteride/dutasteride group. Reprinted from Debruyne et al[40] with permission from the European Association of Urology.*

The consensus was that long-term (4-year) treatment with dutasteride results in continuing improvement of symptoms and peak urinary flow. Earlier initiation of dutasteride therapy results in greater improvements from baseline at 4 years in symptoms and peak urinary flow compared with patients who were initiated on dutasteride therapy at 2 years.

Reissigl and associates[41] evaluated the efficacy and safety endpoints in patients with chronic prostatitis (CP)/chronic pelvic pain syndrome (CPPS) (category III A/B) treated with *Serenoa repens*.

A multicenter study suggests that Permixon® may provide clinical benefit in patients with category IIIA/B chronic pelvic pain syndrome.

Men with category IIIA/B CPPS were prospectively enrolled in 2 institutions and randomized to *Serenoa repens* (Permixon®; Pierre Fabre Medicament, Castres, France) and matched with a placebo control group. Both groups were comparable in terms of age, prostate volume, and PSA. Based on efficacy parameters including Patients Subjective Global Assessment (SGA); the total National Institutes of Health (NIH) Chronic Prostatitis Symptom Index (CPSI); the pain, voiding and quality of life/impact domains of the

CPSI; safety data; PSA; and prostate volume), the response to therapy was evaluated at 6 and 12 weeks, 6 months, 12 months, and 18 months after treatment.

Results report 142 patients who were enrolled (72 *Serenoa repens*; 70 control group). By 12 and 18 months, 76.4% and 71.8% in the active group (*Serenoa repens*) had at least mild improvement (35%–50% improvement) of the SGA and NIH-CPSI versus 24.3% and 18.5% in the control group. Furthermore, 55.7% and 52.6% reported moderate or marked improvement (50% or greater improvement) versus 18.8% and 14.7%, respectively, of patients in the control group.

At 18 months, 68.4%, 56.6%, and 54.7% of patients in the active group demonstrated a 50% or greater improvement in IPSS, Qmax, and QoL score, respectively, compared with 15.2%, 9.1%, and 11.6%, respectively, in the control group. Overall, a 30% reduction of the NIH-CPSI score was observed in the active group versus 6.3% in the control group. Prostate volume did not change significantly in either group. However, PSA decreased by 18% in the active group at 18 months whereas PSA did not differ from baseline in the control group.

This multicenter study suggests that Permixon® may provide clinical benefit in patients with category IIIA/B CPPS. A moderate/marked improvement of the SGA and NIH-CPSI is observed in over 60% of patients. The decrease in serum PSA in CP/CPPS patients treated with *Serenoa repens* (not observed in men with BPH) suggests a different action pathway.

Intervention Therapy / Minimally Invasive Intervention Therapy

On minimally invasive therapy for BPH, Seitz and colleagues[42] presented results from a multicenter European study for the evaluation of the long-term efficacy, safety, and retreatment rates of targeted high-energy transurethral microwave thermotherapy (TUMT) in patients with lower urinary tract symptoms due to BOO and identified predictors of retreatment in patients undergoing TUMT.

In this comparative study, 657 patients with symptomatic BPH were available and evaluated with a follow-up of 2 to 6 years (mean, 3.9 ± 2 years). Patient evaluation included determination of IPSS, OSS, ISS, Qmax, and QoL score, total and TZ prostate volume, serum PSA, and percentage free PSA prior to TUMT and at periodic intervals up to 6 years and a urodynamic investigation pre-TUMT and 3 years thereafter.

Bachmann and associates demonstrated that 80 W high-power KTP laser vaporization is safe and efficient for men with symptomatic benign prostate hyperplasia.

By 2 and 3 years, 78.4% and 75.8%, 64.7% and 63.5%, 84.3% and 84.7% of patients demonstrated a 50% or greater improvement in IPSS, Qmax, and QoL score, respectively, compared with 51% and 49.6%, 62.6% and 59.8%, 66.5% and 63.3%, respectively, by 5 and 6 years. At 3 years follow-up, urodynamic results were available in 188 patients. In these, maximum detrusor pressure (Pdetmax), Pdetmax at maximal flow, and Schaefer score decreased by 42.3 cm H_20, 29.5 cm H_20, and 1.7 points, respectively. At 6 years, the actuarial rate of retreatment was 28.2% (95% CI, 22.0-31.5%) compared with 20.5% (95% CI, 18.4-25.0%) at 3 years. Higher retreatment rates correlated with TZ volumes greater than 50 cc or less than 20 cc, PSA less than 2 ng/mL, and the presence of an endovesical lobe greater than .5 cm. In a multivariate logistic regression model that took account of differences in various pretreatment clinical and biochemical parameters, pre-TUMT PSA, TZ volume, and OSS (in declining order) did correlate with a significantly higher probability of symptoms and QoL (OR = 31.7).

It was concluded that in patients with LUTS due to BOO, TUMT provides a suitable option for improvement of their condition. Overall, 78.4% and 51% will observe a 50% or greater improvement in IPSS at 3 and 6 years, respectively. Retreatment will be required in 28% at 6 years. Higher retreatment rates correlated with TZ volumes greater than 50 cc or less than 20 cc, PSA less than 2 ng/mL, and the presence of an endovesical lobe greater than .5 cm.

Regarding minimal surgery for lower urinary tract, potassium titanyl phosphate (KTP) lasers were validated in 2 studies. The Green Light PV™ system (Laserscope, San Jose, CA) delivers an average of 80 W power and results in rapid and efficient vaporization of the prostate in an almost bloodless environment, thanks to the unique properties of the KTP laser employed.

Barber and associates,[43] from King's College, London, UK, reported on the safety and effectiveness of this new procedure in the first 30 patients, with 6 months follow-up, and discussed the exciting possibilities offered by Green Light PVP (photoselective vaporization of the prostate), having operated on over 100 patients.

Their experience is based on 30 patients on the routine waiting list for TURP, who were offered this new procedure (mean age, 66 years; mean prostate volume, 60 mL). All procedures were performed under general anesthetic in the day surgery unit,

using a 22 Ch continuous flow cystoscope and sterile water as the irrigation fluid.

Eighty watts of KTP laser energy were delivered in the noncontact mode via a side firing ADDStat™ laser fiber (Laserscope) under direct vision. Following protocol, the first 20 patients had an 18 Ch 2-way catheter at the end of the procedure. The placement of a catheter in the next 10 patients was at the surgeons' discretion. All catheters were to be removed 15 hours postoperatively. The first 10 patients stayed 1 night in the hospital for observation; all except 2 of the next 20 patients were discharged home within 4 hours of the procedure.

The authors commented that no patient required postoperative irrigation and 90% voided successfully on initial removal of the catheter. Three of the last 10 patients voided successfully and were discharged directly from the day unit, having had postoperative catheter sited.

At 6 months, results indicated significant improvement in lower urinary tract symptoms from preoperative figures in terms of mean IPSS (22.4 to 7), QofL score (4.6 to 1.3), Qmax (8.3 to 19.5 mL/s), and postvoid residual volume (117.5 to 29 mL). Erectile function as quantified by the International Index of Erectile Function-5 score was, on average, unchanged at 6 months and of those sexually active (n = 18), 55% described retrograde ejaculation.

Complications included bladder neck stricture (7%) and urinary tract infection (7%). Postoperative estimation of prostate volume in 5 patients demonstrated a 48% mean decrease.

High-power KTP laser vaporization of the prostate is safe, effective, and can be performed in the day care setting with rapid discharge. Furthermore, in selected cases the procedure may be catheterless. Results at 6 months demonstrate sustained improvements in LUTS with maintenance of erectile function, and transrectal ultrasound estimations indicate substantial tissue removal. Further experience has demonstrated similar efficacy of this procedure in very large prostates (up to 250 g) and confirm its status as a new challenge to the established surgical options.

Bachmann and coworkers,[44] from the University of Basel, Switzerland, studied the clinical feasibility and efficiency of 80 W KTP laser vaporization of the prostate in patients with symptomatic BPH and PCa.

One hundred ten patients underwent the operation utilizing photoselective KTP laser vaporization with an 80 W power setting. All consecutive patients, independent of a history of chronic urinary retention or chronically indwelling catheter, were included. The clinical evaluation included transrectal ultrasound, residual urine volume (Vres) measurement, IPSS, and Qmax. A follow-up of 6 months was presented.

No major complication occurred intra- or postoperatively, specifically no intra- or postoperative transfusion, TUR-syndrome, fistula, or capsule perforation. The indwelling catheter was removed on average 1.8 ± 1.2 days (range, 1–6 days) after operation. Overall, 18 patients (16%) were discharged with a transurethral or suprapubic catheter. In all patients, the catheter was removed within 1 month after operation. IPSS (mean) decreased from 18.7 preoperatively to 11.4, 10.3, 7.4, and 6.3 at time of discharge, 1, 3 and 6 months follow-up, respectively; Qmax (mean) increased from 10.9 mL/s preoperatively to 13.0, 19.5, 18.4, and 21.1 mL/s at time of discharge, 1, 3, and 6 months follow-up; Vres (mean) decreased from 183 mL preoperatively to 86.9, 26.3, 19.7, and 28.7 mL at time of discharge, 1, 3, and 6 months follow-up, respectively. To date no reoperation was necessary.

The authors conclude that their short-term results are very encouraging and demonstrate that 80 W high-power KTP laser vaporization is safe and efficient for men with symptomatic BPH. With the 80 W KTP laser, instantaneous debulking of prostate tissue is obtained with a reliable relief from obstructive voiding symptoms. Long-term follow-up is in progress and is hoped to confirm these results.

Anagnostou and coworkers reported on the safety and outcome of a large number of multiple puncture percutaneous nephrolithotomies.

Minimally Invasive Surgery in Other Areas

Percutaneous Surgery

Minimally invasive surgery in urology is gaining ground in a number of areas. Patients with a hereditary form of phaeochromocytoma develop multiple tumors at a young age and are prone to recurrences. Nambirajan and colleagues[45] presented laparoscopic partial adrenalectomy cases that obtained removal of the tumor, preservation of the adrenal cortical function, and avoidance of hormonal replacement therapy. It is feasible to perform a second adrenal sparing surgery laparoscopically for recurrences, which is illustrated in 4 cases (Table 2).

Laparoscopic partial adrenalectomy was feasible in all but 1 patient despite previous surgery. There was no need for conversion to open surgery. There were no intra- or postoperative complications. Histology confirmed phaeochromocytoma in all patients and there were no malignancies. At follow-up, blood pressure and urine catecholamines were within normal

Table 2
Partial Adrenalectomy Cases that Obtained Removal of the Tumor, Preservation of the Adrenal Cortical Function, and Avoidance of Hormone Replacement Therapy

Patient	Age	Sex	Syndrome	Adrenal Phaeochromocytoma Size (cm)	Previous Surgery	Laparoscopic Surgery
1	60	F	VHL	Right 2.5, left 2.0 Left retro peritoneum 3.5, lateral to inferior mesenteric artery, near aortic bifurcation, 1.0	Open left partial adrenalectomy and exploration of right adrenal and ileocolic region	Left adrenalectomy, right partial adrenalectomy and excision of paragangliomas
2	20	M	VHL	Left recurrent tumors, 4.0 and 2.0	Open left partial adrenalectomy	Left partial adrenalectomy
3	24	F	MEN 2B	Left, 1.5	Partial, then subsequent total adrenalectomy and 2 explorations on left adrenal	Left partial adrenalectomy
4	18	M	VHL	Left, 2.0	Open bilateral partial adrenalectomy	Left partial adrenalectomy

Source: Reprinted from Nambirajan et al.[45] with permission from the European Association of Urology.
Abbreviations: MEN 2B, multiple endocrine neoplasia type IIB; VHL, Von Hippel-Lindau disease.

levels in all patients except 1 (No. 5), who has asymptomatic elevation with a recurrent tumor on the contralateral side. He is under surveillance. Patient 3 was pregnant at 20 weeks of gestation and she completed pregnancy with a full-term baby. None of the patients required steroid replacement.

Laparoscopic partial adrenalectomy is feasible after previous explorations and is technically easier if the previous approach has been laparoscopic as well. Laparoscopy is the ideal approach in patients prone to recurrent tumors.

Regarding percutaneous surgery, Anagnostou and colleagues[46] reported on the safety and outcome of a large number of multiple puncture percutaneous nephrolithotomies, performed in the Scottish Lithotriptor Centre, in Edinburgh, Scotland, over a period of 12 years, trying to establish whether deciding on a multiple puncture is clinically significant and safe. Data analysis takes into consideration variables like stone burden, difficulty of access into the collecting system, patient's anatomical or clinical special features (eg, horseshoe kidneys, pelviureteric junction obstruction, obesity), and stone-free and complications rates, between 2 groups of patients (a multiple puncture group and a single puncture group).

The study by Dugardin and associates concluded that laparoscopic radical nephrectomies can be done safely for T1 and T2 renal tumors and is a minimally invasive alternative to open surgery.

From a large database of 1059 cases of percutaneous surgery between 1991 and March 2002, full data cases contained 810 kidney punctures whereas the vast majority were performed for patients with complex stone disease (eg, staghorn stones). Single puncture cases were 725 and multiple puncture cases were 85 (82 double puncture and 3 triple puncture; see Table 3).

Access difficulties and awkward distribution of calculi in the collecting system are among the factors to provoke a multiple puncture technique. Stone-free status rates are not usually as satisfactory as in straightforward single puncture cases, although clinical benefit may be excellent for a substantial number of patients. Experience in these endourological procedures and expert radiological assistance are essential to ensure low complication rates that are comparable to single-puncture cases, and should these be provided, the decision for that approach must not be discouraged.

In the challenging subpopulation of horseshoe kidney anatomy, Viola and associates[47] provided valuable data from the same center. Horseshoe kidney is the most common congenital renal fusion anomaly. One of its major and more common complications is urolithiasis, reported to occur in 20%–60% of these patients.

Data from 44 patients treated between 1987 and 2002 were reviewed. Average age was 50 years (range, 3–83) and 81% were male.

Extracorporeal shock-wave lithotripy (ESWL) was used to treat 25 patients in 29 renal units; the average stone burden was 19 mm (range, 5–200). The patients underwent an average of 2.9 sessions (range, 1–13) and average follow-up was 36.5 months (range, 1–91). Presenting symptoms were hematuria, urinary tract infection, and loin pain. Nineteen patients from 20 renal units underwent percutaneous surgery: 12 as a primary indication because of large stone burden; 7 after ESWL failure, including obesity and inability to focus on the kidney in 1. Two patients underwent prior stent insertion, 2 had open renal surgery for stones, and 1 had a laparoscopically assisted heminephrectomy. The average stone surface area was 197 mm^2 (range, 6–2400 mm^2). Follow-up data are available for 8 patients and the average follow-up was 42.3 months (range, 3–144).

In the ESWL group, the fragmentation rate was 90% and the 3-month stone-free rate (SFR) was 31%; when combined with fragment size less than 4 mm, this rose to 59%. In 18 patients with a stone burden less than 13 mm, the 3-month SFR was 40% and 70%, respectively. Seven patients did not have a satisfactory response to ESWL and subsequently underwent percutaneous nephrostolithomy (PCNL).

In the PCNL group, the SFR on postoperative day 1 was 75%. Of the 5 patients with remaining fragments, 3 required further percutaneous surgeries, 1 underwent ESWL, and 1 was lost to follow-up. Complications occurred in 4 patients (21%): 1 patient developed septicemia (treated successfully with medical therapy), and 1 case of a pyelo-vascular communication occurred, which required the suspension of the procedure. Two patients needed a prolonged spell with a nephrostomy (3 wk) because of poor drainage on clamping but subsequent nephrostogram showed adequate drainage. No patient needed a blood transfusion. Of the 6 patients previously treated with ESWL, 5 were stone free after one PCNL and the sixth after 2 PCNL procedures. Stone composition was not routinely documented.

Table 3
Safety and Outcome of a Multiple Puncture Percutaneous Nephrolithotomy

	Multiple Puncture Group	Single Puncture Group
Average stone burden	55.9 mm^3	62.54 mm^3
Access difficulty	Easy, 42 (49%)	Easy, 530 (73%)
	Difficult, 39 (46%)	Difficult, 186 (26%)
	Not possible, 2 (2.3%)	Not possible, 8 (1%)
	Abandoned, 2 (2.3%)	Abandoned, 1
No. (%) of patients with special clinical characteristics	61 (71.7%)	504 (69%)
Stone free	28 (3.2%)	405 (56%)
< 3-mm fragments	13 (15%)	87 (12%)
Complications	11 (13%), unsuccessful, 1	70 (9.6%), unsuccessful, 8

Reprinted from Anagnostou et al.[46] with permission from the European Association of Urology.

The authors concluded that stone management in horseshoe kidneys is a challenging procedure; whereas ESWL is effective in some patients, SFR are low and PCNL produces higher SFR with minimal major complications and failed access. PCNL thus appears to be the preferred management option in patients with urolithiasis in horseshoe kidneys.

Laparoscopic radical nephrectomy is now widely accepted as a treatment modality for renal cancers. Dugardin and colleagues,[48] from France, presented a series of 170 laparoscopic radical nephrectomies performed between March 1997 and July 2003.

All procedures were done by a transperitoneal approach. The files were revised retrospectively. Mean follow-up was 26 months (range, 1–77). Mean operative time was 137 minutes (range, 60–280 min). Operative time decreased to 196, 182, 155, 118, 130, 111, and 135 minutes at 1, 2, 3, 4, 5, 6, and 7 years, respectively. Mean blood loss was 260 mL (range, 0–2000 mL). There were 11 conversions (5 because of obesity, 3 because of difficult dissection, 2 because of tumor size, and 1 because of uncontrollable bleeding). Major complications occurred in 9.5% of cases (3 cases of postoperative bleeding requiring the patient to be taken to the operating room, 3 spleen injuries sutured intraoperatively, 1 abscess, 1 splenectomy for uncontrollable bleeding, 1 liver hematoma, 1 pancreatitis with jejunal fistula, 1 immediate evisceration, 1 case of intestinal adhesions requiring an operation at 3 weeks postoperatively, 1 left colic stenosis also requiring surgical correction, 1 peritonitis following perforation of colic diverticulum, 1 reversible radial paralysis, and 1 cardiac insufficiency necessitating admission to intensive care) and minor complications in 36.7% of cases (UTI in 18 patients, abdominal wall hematoma in 14, transfusion in 12, abdominal wall abscess in 11, 5 renal fossa hematomas, 1 postoperative retention, and 1 respiratory infection). Mean hospital stay was 6 days (range, 2–63 days). Mean specimen weight was 496 g (range, 130–1840 g). Mean specimen

size was 5.1 cm (range, 1.9–11 cm). Pathology revealed cancer in 144 patients (clear cell carcinoma in 120, chromophobe in 6, tubulo-papillary in 13, sarcoma in 3, carcinoma of nondefinable histology in 1, and lymphoma in 1) and benign tumor in 26 (oncocytoma in 16, adenoma in 4, benign cyst in 2, hematoma in 1, angiomyolipoma in 2, and myofibroblastic tumor in 1). Pathological stage was pT1, pT2, pT3, and pT4 in 70%, 14%, 16%, and .7%, respectively. One patient had a port site metastasis and a renal fossa recurrence at 2 months postoperatively (Bellini carcinoma).

Their conclusion was that laparoscopic radical nephrectomies can be done safely for T1 and T2 renal tumors and is a minimally invasive alternative to open surgery.

Training in laparoscopy usually requires a long learning curve and to that a novel model of virtual reality laparoscopic and hand-assisted laparoscopic training has been tested by Challacombe and colleagues.[49] The authors commented that with the time devoted to surgical training under constant scrutiny, trainers are looking for novel, reproducible, and validated operative training techniques. Also, UK licensing laws prohibit wet laparoscopic training using live animals and the current dry laparoscopic trainers lack authenticity.

The authors presented the first prototype for virtual reality training in laparoscopic urologic surgery. Based on custom-made computer hardware and programs (beta version module), they are developing a system that allows both urological trainees and consultant urologists to practice, in virtual reality, operations that they are regularly performing in actuality.

This technology involves the surgeon performing a virtual operation with haptic feedback providing the perception of handling tissue. In addition, a virtual hand also integrates haptic technology so that hand-assisted virtual reality laparoscopic nephrectomy can be attempted.

It is hoped that integration with high-resolution imaging from CT and MRI will allow each virtual reality scenario to be tailored to the exact clinical case requiring nephrectomy. Thus, one could perform a virtual operation on the same patient using the actual anatomy before the real case begins. This training tool has the potential to hugely benefit all grades of urological surgeons and may have significant impact on surgery generally. ■

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Main Points

- One study by Fullerton and coworkers concluded that a targeted gene therapy approach with radiolabeled meta-iodobenzylguanidine (MIGB) may produce a promising new treatment for prostate cancer.
- In another study, it was confirmed that the ratio of urinary prostate-specific antigen (PSA) to serum PSA may be a useful test in prostate cancer detection when total serum PSA is between 4 and 10 ng/mL.
- Herkommer and associates concluded that a history of even 1 first-degree relative with prostate cancer significantly increases the probability of detecting prostate cancer in a screening examination, especially in relatives of younger prostate cancer patients.
- Joniau and colleagues investigated the effects of short-term chemopreventive treatment on PSA and clinical management, and concluded that supplement therapy is of interest in patients with a PSA response, as a large subgroup in this study had a PSA decrease.
- Bader and associates addressed the question of whether incidental prostate cancers should be treated by radical prostatectomy or watchful waiting and concluded that radical prostatectomy is justified in all patients with incidental prostate cancer because it gives them a chance of cure.
- The study of Touijer and associates showed that laparoscopic radical prostatectomy provides good short-term function results, with 53% of preoperatively potent patients having intercourse with or without sidenafil citrate at 3 months when both neurovascular bundles were preserved. Seventy-five percent of patients were socially continent.
- The most relevant finding in a series by Navarrete and coworkers is that open surgery has to be applied more frequently than 10 years ago due to the progressive increase in prostate volume not affected by medical therapy.

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